Affinity-Purified, Mixed Monospecific Crotalid Antivenom Ovine Fab for the Treatment of Crotalid Venom Poisoning

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Study objective: To test the efficacy and safety of a new antivenom, affinity-purified, mixed monospecific crotalid antivenom ovine Fab, in human subjects with minimal or moderate crotalid envenomation.

Methods: We conducted a prospective multicenter clinical trial of 11 patients 10 years or older with progressive manifestations after mild to moderate crotalid snakebite. After giving their consent, subjects received four to eight vials of study drug and were then repeatedly examined over 48 hours and at 7 and 14 days after discharge. Each patient's clinical condition was evaluated serially with the use of a validated severity score, as well as on the basis of the investigator's assessment.

Results: In all 11 subjects the antivenom was judged by the investigator to have had a beneficial response. The severity score for each patient remained the same or decreased over the first 4 hours. However, two subjects demonstrated worsened condition 12 to 15 hours after antivenom administration. In no subject did an allergic reaction develop.

Conclusion: In this patient group, affinity-purified, mixed monospecific crotalid antivenom ovine Fab was associated with a halt of progressive crotalid venom poisoning. Initial safety data are promising but must be addressed further in subsequent studies.

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INTRODUCTION

Crotalid snakebite is an unusual but important cause of injury in the United States. Rattlesnakes and cottonmouth and copperhead snakes inhabit nearly every state and bite approximately 7,000 people each year, resulting in several deaths.[1]

Antivenin (Crotalidae) Polyvalent [Wyeth] is the only antidote commercially available for the treatment of crotalid bite. Although the Wyeth antivenom was a major advance when introduced 40 years ago, it is well known that the antivenom causes serious adverse reactions, including anaphylaxis. The true incidence of anaphylaxis is uncertain, but several deaths have occurred. Other acute reactions—rash, hypotension, wheezing, and phlebitis—occur in about 20% of patients.[2] Also, most patients who receive the Wyeth antivenom experience serum sickness, a type III hypersensitivity reaction that causes malaise, fever, chills, arthralgia, and diffuse rash.[2,3]

The allergenicity of Antivenin (Crotalidae) Polyvalent may be caused by IgG(T), a highly glycosylated immunoglobulin G produced by horses immunized with snake venom. Other components of horse serum that remain in the product are another potential cause.[4] Purification of the Wyeth antivenom was shown to reduce its immunogenicity many years ago,[5] but an improved version was never introduced.

Figure.
Study schematic.

All Patients with Crotalid Bites
↓
Inclusion/Exclusion Screening
↓
Baseline Assessment of Patients
Investigator's Assessment
Snakebite Severity Score
Laboratory Tests
↓
First Dose of Study Antivenom (Four Vials)
↓
Second Dose of Study Antivenom, if needed (Four Vials)
↓
Repeat Assessments: 1, 4, and 12 Hours After Infusion
Investigator's Assessment
Snakebite Severity Score
Laboratory Tests
↓
Hospital Discharge: 48 Hours
↓
Follow-up Visits: 7 and 14 Days
Investigator's Assessment
Assessment of Late Reactions
Laboratory Tests

A new antivenom—affinity-purified, mixed monospecific crotalid antivenom ovine Fab—is produced in a manner similar to digoxin immune Fab (Digibind; Burroughs-Wellcome). Sheep are immunized rather than horses, eliminating the production of IgG(T). The ovine immune serum is then treated with papain to produce antibody fragments (Fab), eliminating the immunogenic Fc portion of the antibody. Finally, the new antivenom is purified to remove non-neutralizing components of ovine serum. Of almost 1,000 patients treated with Digibind in drug trials and in a post-marketing surveillance study, true anaphylaxis has not been noted.[6,7] The findings of animal studies indicate that the new antivenom is also more potent than the current antivenom. When tested with 14 different crotalid venoms, the new antivenom averaged 5.2 times (range, 3.0 to 11.7) more potent than the Wyeth antivenom.[8]

This trial was a pilot test of the efficacy and safety of the new antivenom in human subjects with minimal or moderate crotalid envenomation.

MATERIALS AND METHODS

Eleven patients were enrolled in this prospective, open-label, multicenter trial from August through November 1993 (Figure). The study was approved by the institutional review board at each site. After enrollment and standardized initial assessment (history, physical examination, and laboratory tests) and informed consent, each patient received an intravenous dose of the study antivenom. The data included in this report were collected directly from case report forms completed by each investigator during patient care. These data were not monitored by the manufacturer.

Each patient met all inclusion criteria: (1) minimal or moderate North American crotalid envenomation (Table 1) in the 6 hours preceding presentation, (2) age 10 years or older, and (3) progression of envenomation syndrome. "Progression" was defined as documented worsening of any evaluation parameter used in grading the envenomation: local injury, coagulation laboratory abnormality, or systemic symptoms or signs. Progression had to occur under the investigator's direct observation.

Treatment was partially standardized. Antivenom had to be administered in an ED or ICU. Narcotic pain medications were allowed, but analgesics with antiplatelet activity were not. RBC or platelet transfusions, antihistamines, corticosteroids, and antibiotics were not allowed unless the following criteria were met: antibiotics were allowed only if clear clinical or bacteriologic evidence of infection existed, and antihistamines and corticosteroids were allowed only in subjects with early or late serum reactions.

Exclusion criteria included (1) bite by the copperhead snake *(Agkistrodon contortrix);* (2) lack of apparent envenomation or lack of progression; (3) severe venom poisoning; (4) infusion of more than one vial of Antivenin (Crotalidae) Polyvalent; (5) presence of major organ disease or electrocardiographic or radiographic abnormalities that, in the investigator's judgment, would interfere with evaluation of the patient; (6) history of hypersensitivity to any sheep-derived product, (7) any use of systemic corticosteroids, use of any experimental drug in the 4 weeks preceding study enrollment, or use of other medication contraindicated in the judgment of the investigator; (8) pregnancy or lactation; (9) previous enrollment in the study; and (10) inability to give informed consent.

Each vial of affinity-purified, mixed monospecific crotalid antivenom ovine Fab (Therapeutic Antibodies, Incorporated) contained 750 mg Fab and 90 mg NaCl. Each vial was reconstituted in 10 mL of normal saline solution. Each patient received an initial dose of four vials diluted in normal saline solution to a final volume of 250 mL. This dose was administered over 60 minutes. If clinical signs or laboratory values continued to worsen after the first dose, another four vials were permitted. When two doses were ineffective, treatment was considered to have failed.

Hospital evaluation was continued for 48 hours, with outpatient follow-up visits at 7 and 14 days. The clinical condition of each patient was assessed at baseline and 1, 4 and 12 hours after antivenom infusion using two measures. The primary assessment was conducted with the use of the snakebite severity score, a validated measure of limb swelling, coagulation tests, and gastrointestinal, neurologic, and cardiac signs (Table 2).[9] A secondary measure, the investigator's assessment, was used to substantiate the severity score and to assure that the score was clinically relevant. The investigator judged the patient's clinical response as (1) clinical improvement (pretreatment signs and symptoms associated with the bite site improved or progression was arrested after treatment with antivenom), (2) clinical failure (signs and symptoms associated with the bite worsened despite antivenom treatment), and (3) evaluation not possible (investigator unable to evaluate the response).

Blood was drawn for measurement of blood chemistries, as well as hematologic and coagulation parameters, at baseline; 1, 4, 12, 24, and 48 hours after antivenom administration; and whenever assay was deemed clinically necessary by the investigator. Acute antivenom reactions were evaluated during the antivenom infusion and the subsequent 2 hours.

Each patient was hospitalized for 48 hours, longer if, in the investigator's judgment, a longer stay was clinically indicated. All patients were scheduled for follow-up visits at 7 and 14 days after discharge. During these visits clinical and laboratory tests were repeated and the patient was assessed for the occurrence of delayed hypersensitivity. Each patient was given a diary to record symptoms that occurred between visits.

All patients who received the study drug and completed 12 hours of hospitalization were eligible for efficacy evalu-

Table 1.
Demographic description of enrolled patients.

Patient No.	Age (Years)	Sex	Envenomation Severity	Bite Site	Ethnicity
1	71	M	Moderate	Tucson	White
2	50	F	Moderate	San Diego	White
3	13	M	Moderate	Phoenix	Hispanic
4	26	M	Moderate	Phoenix	White
5	34	M	Moderate	Phoenix	White
6	75	M	Moderate	Phoenix	Native American
7	55	M	Moderate	Georgia	White
8	33	M	Moderate	Tucson	White
9	32	M	Moderate	Tucson	White
10	42	M	Moderate	Tucson	White
11	23	M	Moderate	Tucson	White

Minimal envenomation: Swelling, pain, and ecchymosis limited to the immediate bite site. Systemic symptoms and signs absent. Coagulation parameters normal, with no clinical evidence of bleeding. **Moderate envenomation**: Swelling, pain and ecchymosis involving less than a full extremity—or, if bite was sustained on trunk, head, or neck, extending less than 50 cm. Systemic symptoms and signs may be present but not life threatening, including but not limited to nausea, vomiting, oral paresthesia or unusual tastes, mild hypotension (systolic blood pressure greater than 90 mm Hg), mild tachycardia (heart rate >150), and tachypnea. Coagulation parameters may be abnormal, but no clinical evidence of bleeding is present. Minor hematuria, gum bleeding, and nosebleeds do not disqualify the patient from classification in this category if they are not considered severe in the investigator's judgment. **Severe envenomation**: Swelling, pain, and ecchymosis involving more than an entire extremity or threatening the airway. Systemic symptoms and signs are markedly abnormal, including severe alteration of mental status, severe hypotension, severe tachycardia, tachypnea, and respiratory insufficiency. Coagulation parameters are abnormal, with serious bleeding or severe threat of bleeding.

ation. "Efficacy" was defined as a decrease or no change in severity score. All patients given the study drug were eligible for evaluation of early reactions. All patients given the study drug who completed both follow-up visits were eligible for evaluation of delayed reactions.

RESULTS

Eleven patients were enrolled (Table 1); all met the inclusion criteria for evaluation of efficacy. No patient was excluded. Five patients received four vials and six patients received eight vials of study antivenom. The mean severity score for all patients was 3.9±2.2 (mean±SD) before antivenom administration; 12 hours after administration the mean score was 2.6±1.0 (Table 2).

The investigators judged that all patients were clinically improved after antivenom infusion. Examination of individual scores, however, showed that patients 1 and 8 had increased severity scores after initial improvement for several hours. Patient 1 received another four vials of the study antivenom; patient 8, who had already received eight vials of the study antivenom (maximum allowed by the protocol), received additional treatment with 10 vials of Antivenin (Crotalidae) Polyvalent. Both demonstrated improvement after the supplemental antivenom infusion. Patient 10 was found to have a coagulopathy at the second follow-up visit despite apparent resolution during hospitalization. This patient was not treated with additional antivenom, and the coagulopathy resolved over several days.

Two patients had thrombocytopenia at presentation. Both demonstrated normal platelet counts after treatment with the study antivenom, but in three patients mild thrombocytopenia developed during the course of illness (Table 3). None required further therapy, and all were normal by the second follow-up visit.

Four patients had prolonged prothrombin time at presentation. All responded well to the study antivenom, and all had normal values at discharge. Recurrent prolongation developed in one patient at 7 days; it had resolved by the 14-day visit (Table 4). Two patients had hypofibrinogenemia at presentation, and it developed in two more during antivenom infusion (Table 5). All patients had a normal or near-normal fibrinogen concentration at discharge, but three patients had recurrence of hypofibrinogenemia at subsequent follow-up visits.

All 11 tolerated the study drug well, and no acute reactions were reported. Three patients did not return for follow-up visits and were excluded from analysis of late reactions (serum sickness). In none of the remaining eight patients did serum sickness or other complications develop. Two of the truant patients were contacted by telephone: one had no symptoms, but patient 8 experienced symptoms consistent with a late allergic reaction. This patient had received 10 vials of Antivenin (Crotalidae) Polyvalent in addition to the study antivenom.

DISCUSSION

In 1985, Lindsey challenged the use of Wyeth antivenom because no controlled study of efficacy and safety had been

Table 2.
Severity score and corresponding investigator's assessment.

Patient No.	No. of Vials	Initial Severity Score	Severity Score at End of Infusion	Severity Score After Infusion		
				1 Hour	4 Hours	12 Hours
1	8	2	2	2 (CI)	2 (CI)	3 (CF)
2	8	6	6	6 (CI)	3 (CI)	3 (CI)
3	8	4	3	3 (CI)	3 (CI)	3 (CI)
4	4	3	2	2 (CI)	2 (CI)	2 (CI)
5	4	3	2	2 (CI)	2 (CI)	2 (CI)
6	4	3	4	3 (CI)	3 (CI)	2 (CI)
7	4	6	2	2 (CI)	2 (CI)	2 (CI)
8	8	3	3	3 (CI)	3 (CI)	5 (CF)
9	8	2	5	3 (CF)	3 (CI)	3 (CI)
10	8	9	5	5 (CI)	5 (CI)	3 (CI)
11	4	2	2	2 (CI)	1 (CI)	1 (CI)
Mean±SD	6.2±2.1	3.9±2.2	3.3±1.5	3.0±1.3	2.6±1.0	2.6±1.0

CI, investigator's judgment of clinical improvement: pretreatment signs and symptoms associated with the bite site improved, or progression was arrested after treatment with antivenom; **CF,** investigator's judgment of clinical failure: signs and symptoms associated with the worsening of envenomation despite antivenom treatment.

performed.[10] Our trial provides the first prospective evidence in human subjects that antivenom may be an effective treatment for venom poisoning caused by North American crotalid snakes. We used a validated severity score, as well as the investigator's clinical assessment: a clinically relevant, albeit more subjective, judgment. Both measures indicated that all patients were improved at the 4-hour assessment time, despite documentation that each patient's condition had worsened immediately before antivenom administration.

Although their condition was initially improved after study antivenom administration, three patients subsequently worsened: swelling recurred in patients 1 and 8, and recurrent coagulopathy developed in patient 10. Both cases of recurrent swelling occurred 15 to 18 hours after antivenom administration, whereas the return of coagulopathy was discovered at the 1 week follow-up visit. Patient 10 never had completely normal coagulation parameters before hospital discharge (Table 5). Thus it is likely that this patient's coagulopathy worsened after discharge but was not discovered until the scheduled follow-up visit.

At least four possible explanations exist for the recurrence of local manifestations or coagulopathy. First, the amount of venom injected may have simply overwhelmed the capacity of the antivenom to neutralize all venom components. It may be that the antivenom neutralized circulating venom initially but, as continued absorption occurred, no unbound antivenom remained, thereby allowing venom injury to recur. A variant of the same concept involves the pharmacokinetics of Fab. The elimination half-life of digoxin immune Fab in human beings is estimated at 16 to 30 hours.[11,12] In a patient with normal kidney function, much of the study antivenom would be eliminated within 18 hours. If absorption of venom from tissue stores continued, the venom could act unopposed because the antivenom would largely have been excreted. This theory is plausible, but it assumes prolonged venom absorption from its site of deposition, a concept that has not been addressed in the medical literature for North American crotalid snakes. Indirect evidence of prolonged absorption of crotalid venom in animals and human beings is available.[13,14] Furthermore, Ho et al[15] demonstrated that recurrent manifestations caused by the bite of the Malayan pit viper (*Calloselasma rhodostoma*) coincided with recurrence of unbound venom levels. These authors also hypothesized that the recurrence was due to prolonged absorption of venom.

Second, it is possible that venom components became unbound from the antivenom, allowing venom injury to recur. Digoxin-immune Fab is the only Fab preparation in which recurrence of free drug level has been demonstrated. Free digoxin levels drop to zero within minutes of digoxin Fab administration, but recurrence of free digoxin levels has been noted as early as 12 to 24 hours after Fab administration.[12] Because the molecular weight of venom components is much larger than that of digoxin, it is likely that Fab–venom complexes are not excreted in the urine. Fab–venom complexes are likely removed by the reticuloendothelial system, thereby prolonging half-life in the circulation. Thus the cause of recurrence may be revealed by the con-

Table 3.
Platelet count (cells/mm^3×10^3).

Patient No.	Before Antivenom Infusion	End of Antivenom Infusion	After Antivenom Infusion				
			1 Hour	4 Hours	48 Hours	7 Days	14 Days
1	296	278	298	272	228	298	323
2	251	265	260	236	ND	247	300
3	76*	179	171	ND	86*	192	237
4	219	209	211	176	ND	ND	ND
5	336	295	286	298	ND	300	322
6	ND	169	165	158	144	155	328
7	262	199	207	219	217	238	ND
8	201	141	163	210	67*	ND	ND
9	175	167	166	192	120*	125*	279
10	39*	139*	146	182	154	280	256
11	299	294	287	283	214	ND	ND
Mean±SD	215±97	212±60	215±58	223±48	154±62†	229±66	292±36

ND, not determined.
*Abnormal value for reporting laboratory.
†$P<.01$, one-way ANOVA.
Results obtained with Bonferroni's multiple-comparisons test indicated that 48-hour and 14-day samples were significantly different.

trasting half-lives of unbound Fab and the Fab–venom complex. The longer half-life of the complex means it persists in the blood. In the meantime, the unbound Fab has been excreted. If subsequent dissociation of the Fab–venom complex occurs, little or no unbound Fab may be present to neutralize it.

Third, it is possible that venom components absorbed several hours after envenomation are different than those neutralized initially by the antivenom. Snake venom comprises dozens of components. Each component has its own physicochemical characteristics that affect its absorption after a subcutaneous or intramuscular bite. It is therefore likely that some components are absorbed long after others. Perhaps these components are not neutralized by the study antivenom. Delayed absorption would then produce delayed effects if the antivenom did not neutralize these components or if the unbound Fab was excreted before their absorption.

Fourth, it is possible that human antisheep antibodies had developed. For example, if the patient had produced antibodies against the sheep Fab in the antivenom, these antibodies might have interfered with ability of Fab to bind venom components. We believe this to be an implausible cause of recurrence in our patients because this phenomenon requires 7 to 10 days to several weeks to develop.

Although it is important to understand the underlying cause of recurrent venom effects, all potential causes may be addressed by altering the dosing schedule, except, perhaps, the development of antisheep antibodies. For example, the study antivenom may have to be administered repeatedly until all venom has been neutralized. The optimal dosing interval remains to be determined.

Another important finding of this study is the lack of acute or delayed allergic reactions. The currently available antivenom, Antivenin (Crotalidae) Polyvalent is known to produce acute reactions in 20% to 25% of patients and serum sickness in 70% to 80% of patients given five vials or more.[2,3] In a study of 11 patients, therefore, only two or three acute allergic reactions might have been expected, and it is not possible to compare statistically the new antivenom and the Wyeth product. In the case of serum sickness, however, at least seven or eight cases of delayed reaction would have been expected with the Wyeth product; none was observed with the investigational antivenom. Nevertheless, the possibility cannot be excluded.

The main limitation of this trial is its unblinded, noncomparative design. A unblinded trial cannot control for investigator bias. Although we used a validated severity score to control bias, it is likely that some bias was present. It is not possible to determine whether this bias favored or opposed our results. Further, it is possible that each patient would have improved spontaneously without the administration of the study antivenom. Several precautions were taken to minimize this possibility. First, we enrolled only those patients who sustained bites in the 6 hours preceding presentation, to minimize the possibility that the envenomation syndrome was about to subside spontaneously. Second, documented worsening of swelling or coagulation parameters was required for every patient. Although it is conceiv-

Table 4.
Prothrombin time (seconds).

Patient No.	Before Antivenom Infusion	End of Antivenom Infusion	After Antivenom Infusion				
			1 Hour	4 Hours	48 Hours	7 Days	14 Days
1	12.7	13.5	13.2	12.2	11.7	12.7	12.2
2	11.9	13.4	13.2	11.9	ND	10.8	10.7
3	14.0*	12.3	12.2	ND	11.5	11.2	11.3
4	13.8*	14.1*	14.0*	13.9*	ND	ND	ND
5	11.8	12.5	12.2	11.9	11.6	11.1	ND
6	13.8*	14.6*	13.5*	12.9	12.1	12.0	11.8
7	12.0	13.0	13.0	12.0	12.0	12.0	11.0
8	12.0	14.9*	14.7	13.8	12.1	ND	ND
9	12.6	13.8	14.0	14.3	13.1	13.1	13.1
10	18.3*	24.7*	21.0*	15.1*	13.6	22.8*	13.8
11	13.1	13.5	13.1	13.4	11.9	ND	ND
Mean±SD	13.3±1.9	14.6±3.5	14.0±2.4	13.1±1.1	11.7±.6	13.2±4.0	12.0±1.1

*Abnormal value for reporting laboratory.
One-way ANOVA revealed no statistical differences among groups.

able that our patients spontaneously improved, it is extremely unlikely that this occurred in 11 consecutive cases.

Finally, it is also important to note that only patients with snakebites of minimal or moderate severity were enrolled. This was done because this study was the first use of the study antivenom in human subjects. More trials must be performed to ensure that the antivenom is effective and safe in patients with severe envenomation.

Preliminary results indicate that affinity-purified, mixed monospecific crotalid antivenom ovine Fab may be an effective antivenom for the treatment of North American crotalid envenomation of minimal to moderate severity. However, further research is needed to determine optimal dosing intervals. Preliminary safety data are promising, but more widespread use is needed to document safety.

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Table 5.

Fibrinogen concentration (mg/dL).

Patient No.	Before Antivenom Infusion	End of Antivenom Infusion	After Antivenom Infusion				
			1 Hour	4 Hours	48 Hours	7 Days	14 Days
1	382	323	371	318	352	166	405
2	313	290	380	284	ND	246	300
3	304	246	261	ND	342	424	348
4	300	282	321	304	ND	ND	ND
5	180*	171*	188*	205	ND	273	ND
6	204	345	359	348	ND	143*	225
7	294	261	ND	262	296	351	311
8	280	178*	179*	220	361	ND	ND
9	ND	169*	179*	189*	277	143*	257
10	<15*	<15*	<15*	62*	148*	<50*	94*
11	194	173	186	176	180	ND	ND
Mean±SD	246±103	223±94	244±116	236±84	279±85	224±123	277±100

ND, not determined.
*Abnormal value for reporting laboratory.
One-way ANOVA revealed no statistical differences among groups.